

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/28716

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/4709, 31/47; C07D 215/14, 401/10, 413/10  
US CL : 546/167, 172, 173; 514/314, 311, 256, 253.06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
U.S. : 546/167, 172, 173; 514/314, 311, 256, 253.06

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
STN CAS Online Databases FILE REGISTRY, CAPLUS; and EAST, WEST

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6,410,563 B1 (DESCHENES et al) 25 June 2002 (25.06.2002), Columns 26-84.	1-7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

25 January 2004 (25.01.2004)

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
Facsimile No. (703)305-3230

Date of mailing of the international search report

05 MAY 2004

Authorized officer

Alan Rotman *J. Roberts for*  
Telephone No. 703.308.1235

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
1 April 2004 (01.04.2004)

PCT

(10) International Publication Number  
WO 2004/026794 A3

(51) International Patent Classification: A61K 31/4709,  
31/47, C07D 215/14, 401/10, 413/10

(74) Common Representative: MERCK & CO., INC.; 126  
East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(21) International Application Number:  
PCT/US2003/028716

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,  
GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC,  
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,  
MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC,  
SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA,  
UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(22) International Filing Date:  
12 September 2003 (12.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(84) Designated States (*regional*): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SI, SZ, TZ, UG, ZM, ZW),  
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,  
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,  
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,  
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(30) Priority Data:  
60/411,245 17 September 2002 (17.09.2002) US

(71) Applicant (*for all designated States except US*): MERCK  
& CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway,  
NJ 07065-0907 (US).

**Published:**

- with international search report
- before the expiration of the time limit for amending the  
claims and to be republished in the event of receipt of  
amendments

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): BIBA, Mir-  
linda [US/US]; 126 East Lincoln Avenue, Rahway, NJ  
07065-0907 (US). COLLINS, Paul Compton [US/US];  
126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).  
WELCH, Christopher Joseph [US/US]; 126 East Lin-  
coln Avenue, Rahway, NJ 07065-0907 (US). CONLON,  
David, A. [US/US]; 126 East Lincoln Avenue, Rahway,  
NJ 07065-0907 (US). DRAHUS, Antoinette [US/US];  
126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(88) Date of publication of the international search report:  
17 June 2004

*For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.*

(54) Title: REMOVAL OF ALDEHYDE IMPURITY BY REACTIVE POLYSTYRENE RESIN

(57) Abstract: A purification method in the preparation of a substituted 8-arylquinoline, wherein the aryl group at the 8-position contains a substituent substituted-alkenyl group, utilizes a polystyrene-based sulfonylhydrazine reactive resin to remove an aldehyde impurity.

WO 2004/026794 A3



To the European Patent Office

**Entry into the European phase (EPO as designated or elected Office)**

European application number	EP03754525.8
PCT application number	PCT/US2003/28716
PCT publication number	WO04026794
Applicant's or representative's reference	21181

**1. Applicant**

Particulars of the applicant(s) are contained in the international publication or were recorded by the International Bureau subsequent to the international publication.



Changes which have not yet been recorded by the International Bureau are set out here:



**Address for correspondence**

**2. Representative 1**

This is the representative who will be listed in the Register of European Patents and to whom notifications will be made

Name

Horgan, James

Address of place of business

Merck & Co., Inc.,  
European Patent Department  
Terlings Park,  
Eastwick Road,  
Harlow, Essex CM20 2QR,  
United Kingdom

Telephone

(01279) 440 625

Fax

(01279) 440 717

e-mail

TP\_EPatents@Merck.com

Any additional representative(s) is/are listed here:



**3. Authorisation**

An individual authorisation is attached.



A general authorisation has been registered under No:



15466

A general authorisation has been filed, but not yet registered.



The authorisation filed with the EPO as PCT receiving Office expressly includes the European phase.



**4. Request for examination**

Examination of the application under Art. 94 EPC is hereby requested. The examination fee is being (has been, will be) paid.



Request for examination in an admissible non-EPO language:



---

## 5. Copies

One or more additional sets of copies of the documents cited in the supplementary European search report are hereby requested.



Number of additional sets of copies

1

---

## 6. Documents intended for proceedings before the EPO

6.1 Proceedings before the EPO as designated Office (PCT I) are to be based on the following documents:

the application documents published by the International Bureau (with all claims, description and drawings), where applicable with amended claims under Art. 19 PCT



unless replaced by the amendments attached.



*Where necessary, clarifications should be attached as 'Other Documents'*

6.2 Proceedings before the EPO as elected Office (PCT II) are to be based on the following documents:

the documents on which the international preliminary examination report is based, including any annexes



unless replaced by the amendments attached.



*Where necessary, clarifications should be attached as 'Other Documents'*

If the EPO as International Preliminary Examining Authority has been supplied with test reports, these may be used as the basis of proceedings before the EPO.



---

## 7. Translations

Translations in one of the official languages of the EPO (English, French, German) are attached as crossed below:

\* *In proceedings before the EPO as designated or elected Office (PCT I + II):*

Translation of the international application (description, claims, any text in the drawings) as originally filed, of the abstract as published and of any indication under Rule 13bis.3 and 13bis.4 PCT regarding biological material



Translation of priority application(s)



It is hereby declared that the international application as originally filed is a complete translation of the previous application (Rule 38(5) EPC)



\* *In addition, in proceedings before the EPO as designated Office (PCT I):*

Translation of amended claims and any statement under Art. 19 PCT, if the claims as amended are to form the basis for the proceedings before the EPO (see Section 6).



\* *In addition, in proceedings before the EPO as elected office (PCT II):*

Translation of annexes to the international preliminary examination report



---

**8. Biological material**

The invention relates to and/or uses biological material deposited under Rule 28 EPC. ☐

The particulars referred to in Rule 28(1)(c) EPC (if not yet known, the depository institution and the identification reference(s) [number, symbols, etc.] of the depositor) are given in the international publication or in the translation submitted under Section 7 on: ☐

page(s) / line(s)

A copy of the receipt(s) of deposit issued by the depository institution

is attached ☐

will be filed at a later date ☐

A waiver of the right to an undertaking from the requester pursuant to Rule 28(3) EPC is attached. ☐

---

**9. Nucleotide and amino acid sequences**

The items required under Rules 5.2 and 13ter PCT and Rule 111(3) EPC have already been furnished to the EPO. ☐

The sequence listing as part of the description is attached in PDF format. ☐

The sequence listing does not include matter that goes beyond the content of the application as filed. ☐

In addition, the sequence listing data is attached in computer-readable form in accordance with WIPO Standard 25. ☐

The sequence listing data in computer-readable form in accordance with WIPO Standard 25 is identical to the sequence listing in PDF format. ☐

---

**10. Designation fees**

10.1 It is currently intended to pay seven times the amount of the designation fee. The designation fees for all the EPC contracting states designated in the international application are thereby deemed to have been paid (Art. 2 No. 3 RFees). ☒

AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU NL PT RO SE SI SK TR

10.2 The declaration in No. 10.1 does not apply. Instead, it is currently intended to pay fewer than seven designation fees for the following EPC contracting states designated in the international application: ☐

It is requested that no communications under Rule 108(3) EPC be issued in respect of any contracting states not indicated.

10.3 If an automatic debit order has been issued (Section 12), the EPO is authorised, on expiry of the basic period under Rule 107(1)(d) EPC, to debit seven times the amount of the designation fee. If states are indicated in No. 10.2, the EPO will debit designation fees for those states only, unless instructed otherwise before the basic period expires. ☒

---

## 11. Extension of the European patent

This application is also considered as being a request for extension to all the non-contracting states to the EPC designated in the international application with which "extension agreements" were in force on the date of filing the international application. However, the extension only takes effect if the prescribed extension fee is paid.



It is currently intended to pay the extension fee for the following states:

## 12. Automatic debit order



Currency

EUR

The EPO is hereby authorised, under the Arrangements for the automatic debiting procedure, to debit from the deposit account below any fees and costs falling due. For designation fees, see "States". The EPO is also authorised, on expiry of the basic period for paying the extension fees, to debit those fees for each of the "extension states" indicated in "States".

Deposit account number  
Account holder

28050124  
Merck & Co., Inc.

## 13. Reimbursements (if any) should be made to the following EPO deposit account:



Number and account holder

28050124, Merck & Co., Inc.

## 14. Fees

		Factor applied	Fee schedule	Amount to be paid
14-1	002 Search fee	1 (80%)	690.00	552.00
14-2	005 Designation fee	7	75.00	525.00
14-3	006 Examination fee	1	1 430.00	1 430.00
14-4	015 Claims fee	0	40.00	0.00
14-5	020 Basic national fee for an international application	1	90.00	90.00
14-6	055 Additional copy	1	20.00	20.00
Total:			EUR	2 617.00

## 15. Annotations

### 15-1. Note (for EPO) (EP Phase)

Automatic debit procedure (Mr. J. Horgan;  
15/03/2005)  
The European Patent Office is hereby  
authorised to debit account no. 28050124  
with all fees incurred now and in the future.

### 15-2. Note (for EPO) (EP Phase)

Replacement pages (Mr. J. Horgan;  
15/03/2005)  
Replacement pages 14 & 15.

## 16. Signature(s) of applicant(s) or representative

Place: Harlow,  
Date: 17 March 2005  
Signed by: Subject: GB, Merck & Co. Inc., J. Horgan 621  
Issuer: , European Patent Office, European Patent Office CA

Capacity: ( Representative )

For employees (Art. 133(3) EPC) having a general authorisation:

General authorisation No.

---

$-\text{C}(\text{O})\text{N}(\text{C}_0\text{-C}_6\text{alkyl})(\text{C}_0\text{-C}_6\text{alkyl})$ ,  $-\text{NH}-\text{SO}_n(\text{C}_1\text{-C}_6\text{alkyl})$ ,  $-\text{SO}_n(\text{C}_1\text{-C}_6\text{alkyl})$ ,  $-(\text{C}_1\text{-C}_6\text{alkyl})\text{-O-C}(\text{CN})$ -dialkylamino, or  $-(\text{C}_1\text{-C}_6\text{alkyl})\text{-SO}_n(\text{C}_1\text{-C}_6\text{alkyl})$  group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen,  $-\text{OH}$ ,  $-\text{CN}$ ,  $-\text{C}_1\text{-C}_6\text{alkyl}$ ,  $-\text{cycloC}_3\text{-C}_6\text{alkyl}$ ,  $-\text{C}(\text{O})(\text{heterocycloC}_3\text{-C}_6\text{alkyl})$ ,  $-\text{C}(\text{O})\text{-O}(\text{C}_0\text{-C}_6\text{alkyl})$ ,  $-\text{C}(\text{O})$ -aryloxy,  $-\text{C}_1\text{-C}_6\text{alkoxy}$ ,  $-(\text{C}_0\text{-C}_6\text{alkyl})(\text{C}_0\text{-C}_6\text{alkyl})$ amino, cycloalkyloxy, acyl, acyloxy,  $-\text{cycloC}_3\text{-C}_6\text{alkyl}$ ,  $-\text{heterocycloC}_3\text{-C}_6\text{alkyl}$ , aryl, heteroaryl, carbonyl, carbamoyl, or  $-\text{SO}_n(\text{C}_1\text{-C}_6\text{alkyl})$ ;

$\text{R}_2$  and  $\text{R}_3$  independently is an aryl, heteroaryl, H, halogen,  $-\text{CN}$ ,  $-\text{C}_1\text{-C}_6\text{alkyl}$ ,  $-\text{heterocycloC}_3\text{-C}_6\text{alkyl}$ ,  $-\text{C}_1\text{-C}_6\text{alkoxy}$ , carbonyl, carbamoyl,  $-\text{C}(\text{O})\text{OH}$ ,  $-(\text{C}_1\text{-C}_6\text{alkyl})\text{-SO}_n(\text{C}_1\text{-C}_6\text{alkyl})$ ,  $-\text{C}(\text{O})\text{N}(\text{C}_0\text{-C}_6\text{alkyl})(\text{C}_0\text{-C}_6\text{alkyl})$ , or  $-\text{C}_1\text{-C}_6\text{alkyl}$ acylamino group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently an aryl, heteroaryl, halogen,  $-\text{NO}_2$ ,  $-\text{C}(\text{O})\text{OH}$ , carbonyl,  $-\text{CN}$ ,  $-\text{C}_1\text{-C}_6\text{alkyl}$ ,  $-\text{SO}_n(\text{C}_1\text{-C}_6\text{alkyl})$ ,  $-\text{SO}_n(\text{aryl})$ , aryloxy,  $-\text{heteroaryloxy}$ ,  $\text{C}_1\text{-C}_6\text{alkoxy}$ , N-oxide,  $-\text{C}(\text{O})\text{-heterocycloC}_3\text{-C}_6\text{alkyl}$ ,  $-\text{NH-cycloC}_3\text{-C}_6\text{alkyl}$ , amino,  $-\text{OH}$ , or  $-(\text{C}_0\text{-C}_6\text{alkyl})(\text{C}_0\text{-C}_6\text{alkyl})$ amino,  $-\text{C}(\text{O})\text{-N}(\text{C}_0\text{-C}_6\text{alkyl})(\text{C}_0\text{-C}_6\text{alkyl})$  substituent group, wherein each substituent group independently is optionally substituted with  $-\text{OH}$ ,  $\text{C}_1\text{-C}_6\text{alkoxy}$ ,  $-\text{C}_1\text{-C}_6\text{alkyl}$ ,  $-\text{cycloC}_3\text{-C}_6\text{alkyl}$ , aryloxy,  $-\text{C}(\text{O})\text{OH}$ ,  $-\text{C}(\text{O})\text{O}(\text{C}_1\text{-C}_6\text{alkyl})$ , halogen,  $-\text{NO}_2$ ,  $-\text{CN}$ ,  $-\text{SO}_n(\text{C}_1\text{-C}_6\text{alkyl})$ , or  $-\text{C}(\text{O})\text{-N}(\text{C}_0\text{-C}_6\text{alkyl})(\text{C}_0\text{-C}_6\text{alkyl})$ ;

one of  $\text{R}_2$  and  $\text{R}_3$  must be an aryl or heteroaryl, optionally substituted; and

$n$  is independently 0, 1, or 2;

said method comprising:

a step of contacting an untreated solution of the compound represented by Formula (I) with a reactive resin effective to substantially remove the aldehyde represented by Formula (II) from said untreated solution to form the clean solution.

2. The method of claim 1, wherein said solutions are in dimethylformamide.

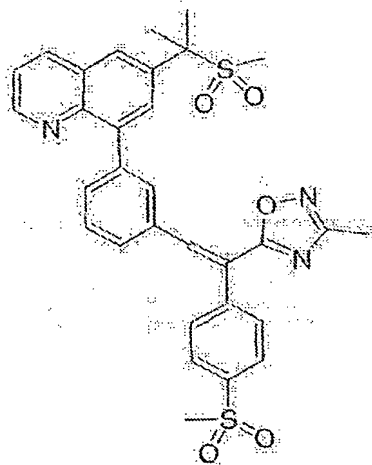
3. The method of claim 1<sup>or 2</sup>, wherein said reactive resin is a solid material bearing a pendant hydrazine moiety.



4. The method of <sup>any previous</sup> claim 3 wherein said reactive resin is a polystyrene-based sulfonylhydrazine.

5. The method of <sup>any previous</sup> claim 4 further comprising a step of:  
adding an antisolvent to said clean solution to yield a crystalline compound represented by Formula (I) substantially free of the aldehyde impurity represented by Formula (II).

6. A method of forming a clean solution of a compound represented by Formula (Ia):



(Ia)

substantially free of an aldehyde represented by Formula (IIa):



Europäisches  
Patentamt

European  
Patent Office

Office européen  
des brevets

### Acknowledgement of receipt

We hereby acknowledge receipt of the form for entry into the European phase (EPO as designated or elected Office) as follows:

Submission number	43872	
PCT application number	PCT/US03/28716	
Date of receipt	17 March 2005	
Your reference	21181	
Applicant		
Country		
Documents submitted	CLMS.PDF application-body.xml package-data.xml	EPF1200.PDF ep-euro-pct.xml
Submitted by	CN=J. Horgan 621,O=Merck & Co. Inc.,C=GB	
Method of submission	Online	
Date and time receipt generated	17 March 2005, 17:40:14	
Digest	4D:93:E9:00:91:9C:EA:1A:9A:46:DF:34:7C:EB:A7:19:70:19:F6:BC	

/European Patent Office/



P. B. 5818 - Patentaan 2  
2280 HV Rijswijk (ZH)  
☎ +31 70 340 2040  
TX 31651 epo nl  
FAX +31 70 340 3016

Europäisches  
Patentamt

Eingangs-  
stelle

European  
Patent Office

Receiving  
Section

Office européen  
des brevets

Section de  
Dépôt

WIPO  
The International Bureau  
34, Chemin des Colombettes  
CH-1211 GENEVA 20  
SWITZERLAND

Datum/Date  
30-03-2005

Zeichen/Ref./Réf. 21181	Anmeldung Nr./Application No./Demande n°/Patent Nr./Patent No./Brevet n°. PCT/US0328716 - EP/03754525.8-1216 / ISA US
Anmelder/Applicant/Demandeur/Patentinhaber/Proprietor/Titulaire Merck & Co., Inc.	

For the aforementioned international application, you are hereby kindly requested to forward to the EPO in its capacity as designated/elected Office:

- ( ) a) the publication of the international search report (Art. 20 PCT)
- (X) b) the copy of the international preliminary examination report (Art. 36(3)(a) PCT)
- ( ) c) the copy (copies) of the priority document(s). If any document is not available and ISA is not EP, please indicate below whether the receiving Office has been requested to transmit the document to the International Bureau (Form PCT/RO/101, Box VI; Rule 17.1(b) PCT).
- ( ) .....

RECEIVING SECTION

Wingenfeld, Susanne

-----

Answer of the International Bureau [IB]:

- ( ) The requested item [a], (b) or c)] is not available with the IB.  
Reason: ..... THE REQUESTED DOCUMENT HAS NOT BEEN RECEIVED AT THE IB

For priority documents [c)] with ISA not EP:

- ( ) The applicant has requested the receiving Office to issue a priority document (Rule 17.1(b) PCT) but the IB has not received it.

EPO -DG 1

The International Bureau

08.04.2005

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

☐ BLACK BORDERS

☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES

☒ FADED TEXT OR DRAWING

☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING

☐ SKEWED/SLANTED IMAGES

☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS

☐ GRAY SCALE DOCUMENTS

☐ LINES OR MARKS ON ORIGINAL DOCUMENT

☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY

☐ OTHER: \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**